

ORIGINAL ARTICLE

Colonoscopic Screening of Average-Risk Women for Colorectal Neoplasia

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ABSTRACT

BACKGROUND

Veterans Affairs (VA) Cooperative Study 380 showed that some advanced colorectal neoplasias (i.e., adenomas at least 1 cm in diameter, villous adenomas, adenomas with high-grade dysplasia, or cancer) in men would be missed with the use of flexible sigmoidoscopy but detected by colonoscopy. In a tandem study, we examined the yield of screening colonoscopy in women.

METHODS

To determine the prevalence and location of advanced neoplasia, we offered colonoscopy to consecutive asymptomatic women referred for colon-cancer screening. The diagnostic yield of flexible sigmoidoscopy was calculated by estimating the proportion of patients with advanced neoplasia whose lesions would have been identified if they had undergone flexible sigmoidoscopy alone. Lesions were considered detectable by flexible sigmoidoscopy if they were in the distal colon or if they were in the proximal colon in patients who had concurrent small adenomas in the distal colon, a finding that would have led to colonoscopy. The results were compared with the results from VA Cooperative Study 380 for age-matched men and women with negative fecal occult-blood tests and no family history of colon cancer.

RESULTS

Colonoscopy was complete in 1463 women, 230 of whom (15.7 percent) had a family history of colon cancer. Colonoscopy revealed advanced neoplasia in 72 women (4.9 percent). If flexible sigmoidoscopy alone had been performed, advanced neoplasia would have been detected in 1.7 percent of these women (25 of 1463) and missed in 3.2 percent (47 of 1463). Only 35.2 percent of women with advanced neoplasia would have had their lesions identified if they had undergone flexible sigmoidoscopy alone, as compared with 66.3 percent of matched men from VA Cooperative Study 380 ($P < 0.001$).

CONCLUSIONS

Colonoscopy may be the preferred method of screening for colorectal cancer in women.

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C OLORECTAL CANCER IS THE SECOND most common cause of death from cancer in the United States,¹ and removal of adenomas appears to reduce the risk of death.² Evidence-based guidelines state that either flexible sigmoidoscopy or colonoscopy may be appropriate for screening asymptomatic patients,³ although the use of screening colonoscopy increased in the United States after the publication of the results of colonoscopic-screening studies.^{4,5} Data from Veterans Affairs (VA) Cooperative Study 380 indicated that the diagnostic yield of flexible sigmoidoscopy for advanced colorectal neoplasia (i.e., adenomas that are at least 1 cm in diameter, villous adenomas, adenomas with high-grade dysplasia, or colon cancer) is 70 percent.⁶ However, since 97 percent of the patients in the VA Cooperative Study 380 were men,⁴ the diagnostic yield of screening colonoscopy has not been defined for women.

Sex-related biologic differences may result in different phenotypic expressions of colorectal cancer between men and women. The age-adjusted prevalence of adenomas^{1,5} and colorectal cancer⁷ is higher among men than among women. Given the lower prevalence of colorectal cancer and adenomas among women, the limited availability of colonoscopic resources, and the economic constraints imposed by a policy of universal colonoscopic screening, recent research⁷ suggests that flexible sigmoidoscopy rather than colonoscopy should be used in low-risk persons — specifically, women below 60 years of age who do not have adenomas in the distal colon. Although editorialists^{8,9} have voiced some support for the use of this approach, they have also stated that additional data in women are needed to facilitate further revision of the guidelines for colorectal-cancer screening⁹ and to educate women about the preferred method.

In this tandem study to VA Cooperative Study 380,⁶ our primary objective was to assess the predictive value of the finding of distal-colon neoplasia (i.e., small adenomas or advanced colorectal neoplasia in the distal colon that would be found during flexible sigmoidoscopy) with respect to advanced neoplasia in the proximal colon of women. Our secondary objectives were to quantify the prevalence and location of advanced colonic neoplasias and small adenomas in asymptomatic women; to compare the prevalence of advanced colonic neoplasia in age-matched men and women with negative fecal occult-blood tests and no family history of colon cancer; and to compare the diagnostic yield

of flexible sigmoidoscopy in men and women. With this information, we sought to determine whether flexible sigmoidoscopy would be a reasonable alternative to colonoscopy in asymptomatic women.

METHODS

STUDY PATIENTS

The protocol was approved by the institutional review board at each participating institution. From July 1, 1999, through December 31, 2002, we enrolled consecutive, average-risk, asymptomatic women who were 50 to 79 years of age and who had been referred for colorectal-cancer screening at four military medical centers: the National Naval Medical Center in Bethesda, Maryland; Walter Reed Army Medical Center in Washington, D.C.; the Naval Medical Center in San Diego, California; and the Naval Medical Center in Portsmouth, Virginia. Asymptomatic women who were 40 to 79 years of age and who had a history of colon cancer in a first-degree relative were also offered enrollment. Similar to VA Cooperative Study 380, oversampling of women with a family history of colon cancer was performed.

To ensure that the study patients were asymptomatic and at average risk, we excluded women who had had a positive fecal occult-blood test within 6 months before referral; those who had had iron-deficiency anemia within 6 months before referral; women who had had rectal bleeding or hematochezia within the preceding 12 months; those with an unintentional weight loss of more than 10 lb (4.5 kg) within the preceding 6 months; women with a history of adenomas, colorectal cancer, inflammatory bowel disease, or hereditary polyposis syndromes; and women who had had normal findings on colonoscopy or barium enema within the preceding 10 years or normal findings on flexible sigmoidoscopy within the preceding 5 years. If patients had not had a complete blood-cell count, a ferritin measurement, or a fecal occult-blood test within the six months before referral, then these tests were performed before study entry. All women were interviewed before study entry to ensure that they met eligibility criteria and to obtain written informed consent.

STUDY PROTOCOL

The women completed detailed questionnaires regarding risk factors before undergoing colonoscopy. These questionnaires quantified demographic and

lifestyle factors that may be associated with advanced colorectal neoplasia or small adenomas.¹⁰⁻¹⁶ Bowel preparation included 4 liters of polyethylene glycol and bisacodyl. Over 99 percent of colonoscopic examinations were performed by gastroenterologists or colorectal surgeons. During colonoscopy, the location of all polyps was defined on the basis of the depth of insertion of the colonoscope and anatomical landmarks, including the hepatic flexure, the splenic flexure, and the junction of the sigmoid and descending colon. These landmarks were identified on the basis of the acute angulation at each junction. Since the diameter of a polyp is frequently misjudged with the use of an open-biopsy forceps,^{17,18} a guidewire (Olympus Colonoscopy Measuring Guidewire)¹⁸ was used to estimate the diameter of a polyp before polypectomy was performed. Since general pathologists may mischaracterize the histologic features of polyps,¹⁹ histologic specimens from every polyp were reviewed by an expert gastrointestinal pathologist who was unaware of the colonoscopic findings and the initial pathological diagnosis. The interpretation of the expert gastrointestinal pathologist was considered final.

The colonoscopic findings were classified on the basis of the most advanced lesion found: cancer, adenoma with high-grade dysplasia, villous adenoma, adenoma of at least 1 cm, adenoma of less than 1 cm, hyperplastic polyp, or normal or other tissue. The most advanced pathological lesion in the entire colon, proximal colon, and distal colon was recorded. To quantify the diagnostic yield of flexible sigmoidoscopy, we used findings in the distal colon as a surrogate for findings on flexible sigmoidoscopy. Since over 50 percent of flexible sigmoidoscopic examinations reach only the junction of the sigmoid and descending colon,^{20,21} the primary definition of the distal colon was the rectum and sigmoid colon. Optimally, a flexible sigmoidoscopic examination would reach the splenic flexure, although this is achieved in a minority of patients.^{20,21} Therefore, an alternative definition of the distal colon as the rectum, sigmoid colon, and descending colon was used for supplemental analysis of the primary end point.

STATISTICAL ANALYSIS

All statistical analyses were performed with the use of SAS software (version 9.2) and Stata software (version 8.0). For the primary end point, we used Fisher's exact test to compare the prevalence of

advanced neoplasia in the proximal colon among patients without distal-colon neoplasia with that among patients with distal-colon neoplasia. If flexible sigmoidoscopy were a perfect screening tool, 0 percent of women without distal-colon neoplasia would have advanced neoplasia in the proximal colon. Assuming a 10 percent prevalence of distal-colon neoplasia and using a two-sided alpha value of 0.05, we estimated that 1450 women would need to be enrolled for the study to have a statistical power of 80 percent to detect an absolute difference of 3 percent in the prevalence of proximal-colon advanced neoplasia between women with distal-colon neoplasia and women without distal-colon neoplasia.

Our secondary objectives included calculation of the diagnostic yield of flexible sigmoidoscopy: the likelihood that a patient with advanced colorectal neoplasia would have this lesion identified if she underwent flexible sigmoidoscopy alone. Flexible sigmoidoscopy can detect this lesion if there is advanced neoplasia in the distal colon or if there is advanced neoplasia in the proximal colon along with small adenomas in the distal colon, since the finding of small adenomas would trigger the performance of colonoscopy, which would then detect the advanced neoplasia in the proximal colon.

To compare the prevalence of advanced neoplasia and the diagnostic yield of flexible sigmoidoscopy among men and women, we matched men from VA Cooperative Study 380 with women from the present study for age, a negative fecal occult-blood test, and the absence of a family history of colon cancer. Matching for these risk factors was performed because a positive fecal occult-blood test and a family history of colon cancer trigger a colonoscopy.³ Chi-square analysis was used to compare the diagnostic yield of flexible sigmoidoscopy and the percentage of women and men with advanced neoplasia in different age groups. When appropriate, we used relative risks to express the difference in the prevalence of advanced neoplasia between any two groups.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

A total of 1593 women were eligible for the study, and 1483 (93.1 percent) participated. Colonoscopy was complete to the cecum in 98.7 percent of the women (1463 of 1483), and no clinically significant complications (i.e., perforation, need for hospital-

ization, or clinically important bleeding) occurred. The mean (\pm SD) age was 58.9 ± 8.1 years, and 15.7 percent of the women had a family history of colorectal cancer (Table 1). Of the 1463 women, 299 (20.4 percent) had a total of 446 neoplastic lesions (Tables 2 and 3). Advanced colorectal neoplasia (i.e., adenomas that were at least 1 cm in diameter, villous adenoma, adenoma with high-grade dysplasia, or invasive colorectal cancer) was present in 72 women (4.9 percent) (Tables 2 and 3), and 227 women (15.5 percent) had small or nonadvanced adenomas. Among the 230 women with a family history of colon cancer, 16 (7.0 percent) had advanced neoplasia and 60 (26.1 percent) had only small adenomas.

The proportion of women with advanced neo-

plasia varied significantly with age ($P=0.01$). Advanced neoplasia was found in 3.3 percent of women who were 50 to 59 years of age (26 of 786), 5.5 percent of women who were 60 to 69 years of age (23 of 420), and 11.7 percent of women who were 70 to 79 years of age (19 of 162). The group of women who were 70 to 79 years old was significantly more likely to have advanced neoplasia than the group of women who were 50 to 59 years old (relative risk, 3.56; 95 percent confidence interval, 1.70 to 7.58; $P=0.002$).

DIAGNOSTIC YIELD OF FLEXIBLE SIGMOIDOSCOPY FOR ADVANCED COLORECTAL NEOPLASIA

If only flexible sigmoidoscopy had been performed in all women, advanced colorectal neoplasia would

Table 1. Characteristics of the 1463 Women.*

Characteristic	All Women (N=1463)	Women with Neoplasia (N=299)	Women with Advanced Neoplasia (N=72)
Age			
40–49 yr (%)†	6.5	5.0	5.6
50–59 yr (%)	53.7	43.8	36.1
60–69 yr (%)	28.7	31.1	31.9
70–79 yr (%)	11.1	20.1	26.4
Mean (yr)	58.9	61.2	62.9
Race or ethnic group (%)			
White	77.0	73.9	69.4
Black	11.6	13.7	18.1
Asian	8.4	10.0	8.3
Hispanic	2.0	1.7	4.2
Other	1.0	0.7	0.0
Height (in.)	64.2	64.2	64.1
Weight (lb)	156.2	158.1	162.6
Body-mass index	26.2	26.6	27.3
≥ 1 First-degree relatives with colorectal cancer (%)	15.7	20.1	22.2
Any regular use of NSAIDs (%)	34.2	30.1	25.0
Any use of hormone-replacement therapy (%)	63.1	58.2	55.6
Current or former smoker (%)	39.0	43.8	51.4
Alcohol consumption (%)‡			
<1 drink/wk	59.0	60.9	62.5
1–6 drinks/wk	29.0	25.4	22.2
7–13 drinks/wk	8.2	10.0	11.1
≥ 14 drinks/wk	3.8	3.7	4.2

* Because of rounding, percentages may not total 100. Race or ethnic group was self-reported. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert height to meters, divide by 39.37. To convert weight to kilograms, divide by 2.2. NSAIDs denotes nonsteroidal antiinflammatory drugs.

† Women who were 40 to 49 years old had a history of colon cancer in a first-degree relative.

‡ For alcohol consumption a drink was defined as one glass of wine, 1 oz (30 ml) of liquor, or one glass of beer.

Table 2. Colonoscopic Findings in the 1463 Women, According to the Most Advanced Lesion.

Finding	No. of Women (%)
No adenomas*	1164 (79.6)
Adenomas	299 (20.4)
Nonadvanced or small adenoma only	227 (15.5)
Advanced colorectal neoplasia†	72 (4.9)
Distal adenoma‡	25 (1.7)
No distal adenoma	47 (3.2)

* Of the 1164 women with no adenomas, 253 had hyperplastic polyps.

† Given these data, the lesion would have been missed in 65.3 percent of women with advanced colorectal neoplasia (47 of 72) if only flexible sigmoidoscopy had been performed. Overall, if only flexible sigmoidoscopy had been performed in all the women, then advanced colorectal neoplasia would have been identified in 1.7 percent (25 of 1463) and missed in 3.2 percent (47 of 1463).

‡ Among the 25 women who had advanced colorectal neoplasia and distal adenoma, 22 (88.0 percent) had advanced colorectal neoplasia in the distal colon and only 3 (12.0 percent) had a small adenoma in the distal colon with advanced colorectal neoplasia in the proximal colon.

Table 3. Characteristics of the 299 Adenomas Found among the 1463 Women.

Characteristic	No. of Women (%)
Nonadvanced or small adenoma only	227 (15.5)
1 lesion	140 (9.6)
2 lesions	55 (3.8)
3 lesions	16 (1.1)
4 lesions	9 (0.6)
>4 lesions	7 (0.5)
Advanced colorectal neoplasia	72 (4.9)
Tubular adenoma ≥10 mm	46 (3.1)
Villous adenoma	26 (1.8)
Adenoma with high-grade dysplasia	9 (0.6)
Invasive cancer	1 (0.1)

have been identified in 1.7 percent (25 of 1463 women) and missed in 3.2 percent (47 of 1463) (Table 2). Since 72 women had advanced neoplasia in the colon, the diagnostic yield of flexible sigmoidoscopy was 34.7 percent (25 of 72 cases detected). Thus, 34.7 percent of women with advanced neoplasia would have had their lesions identified if they had undergone flexible sigmoidoscopy alone. After stratification according to age, there was no significant difference in the diagnostic yield of flexi-

ble sigmoidoscopy between women who were 50 to 59 years old and either those who were 60 to 69 years old or those who were 70 to 79 years old. After stratification according to the presence or absence of a family history of colon cancer, there was no significant difference in the diagnostic yield of flexible sigmoidoscopy between women without a family history of colon cancer and women with a family history of colon cancer (35.7 percent [20 of 56 cases detected] and 31.2 percent [5 of 16], respectively; $P=0.74$).

DISTAL-COLON NEOPLASIA AND ADVANCED NEOPLASIA IN THE PROXIMAL COLON

When the distal colon was defined as the rectum and sigmoid colon, 93.5 percent of women did not have distal-colon neoplasia (1367 of 1462), whereas 6.5 percent (95 of 1462) had advanced colorectal neoplasia or small adenomas in the distal colon. For these analyses, we excluded one woman for whom information about the location of adenoma was not available. The prevalence of advanced colorectal neoplasia in the proximal colon among women with no distal-colon neoplasia was 3.4 percent (47 cases among 1367 women), as compared with 3.2 percent among women with distal-colon neoplasia (3 cases among 95 women, $P=1.00$). If flexible sigmoidoscopy had been performed to the junction of the sigmoid and descending colon in all these women and the finding of distal colorectal neoplasia had triggered a colonoscopy, then 94.0 percent of cases of advanced colorectal neoplasia in the proximal colon would have been missed (47 of 50).

Among women without a family history of colon cancer, the prevalence of advanced colorectal neoplasia in the proximal colon was similar for women without distal-colon neoplasia and women with distal-colon neoplasia (3.1 percent [36 cases among 1156 women] and 3.9 percent [3 cases among 77 women], respectively; $P=0.70$). Among women with a family history of colon cancer, the prevalence of advanced colorectal neoplasia in the proximal colon was higher among women without distal-colon neoplasia than among women with distal-colon neoplasia, although this difference was not significant (5.2 percent [11 cases among 211 women] and 0 percent [0 cases among 18 women], respectively; $P=0.32$).

When the distal colon was defined as the rectum, sigmoid colon, and descending colon, 90.6 percent of women did not have distal-colon neoplasia (1324 of 1462), whereas 9.4 percent had advanced colo-

rectal neoplasia or small adenomas in the distal colon (138 of 1462). With the use of this expanded definition of the distal colon, the prevalence of advanced colorectal neoplasia in the proximal colon was 2.7 percent among women without distal-colon neoplasia (36 cases among 1324 women) and 2.2 percent among women with distal-colon neoplasia (3 cases among 138 women, $P=1.00$). If flexible sigmoidoscopy had been performed to the splenic flexure in all these women and the finding of distal colorectal neoplasia had triggered a colonoscopy, then 92.3 percent of cases of advanced colorectal neoplasia in the proximal colon would have been missed (36 of 39).

PREVALENCE OF ADVANCED NEOPLASIA IN MEN AND WOMEN

In VA Cooperative Study 380, the prevalence of advanced neoplasia among men with a negative fecal occult-blood test varied significantly according to age ($P<0.001$): it was 4.6 percent among men 50 to 59 years old (40 cases among 863 men), 10.8 percent among men 60 to 69 years old (132 cases among 1217 men), and 11.4 percent among those who were at least 70 years old (55 cases among 481 men). As compared with the group of men who

were 50 to 59 years old, the group of men who were 60 to 69 years old were significantly more likely to have advanced neoplasia (relative risk, 2.34; 95 percent confidence interval, 1.66 to 3.30), as were the men who were at least 70 years old (relative risk, 2.47; 95 percent confidence interval, 1.67 to 3.65). After matching men and women with a negative fecal occult-blood test and the absence of a family history of colon cancer, we found that men were more likely to have advanced neoplasia than women (8.6 percent [190 of 2206] vs. 4.5 percent [54 of 1198]; relative risk, 1.91; 95 percent confidence interval, 1.42 to 2.56; $P=0.002$) (Fig. 1).

DIAGNOSTIC YIELD OF FLEXIBLE SIGMOIDOSCOPY IN MEN AND WOMEN

Among men and women who were matched for a negative fecal occult-blood test and the absence of a family history of colorectal cancer, the diagnostic yield of flexible sigmoidoscopy was significantly higher in men ($P<0.001$). A total of 66.3 percent of men (126 of 190) would have had advanced neoplasia detected if flexible sigmoidoscopy alone had been performed, as compared with only 35.2 percent of women (19 of 54). Figure 2 provides a comparison of the diagnostic yield of flexible sigmoidoscopy for men and women, stratified according to age.

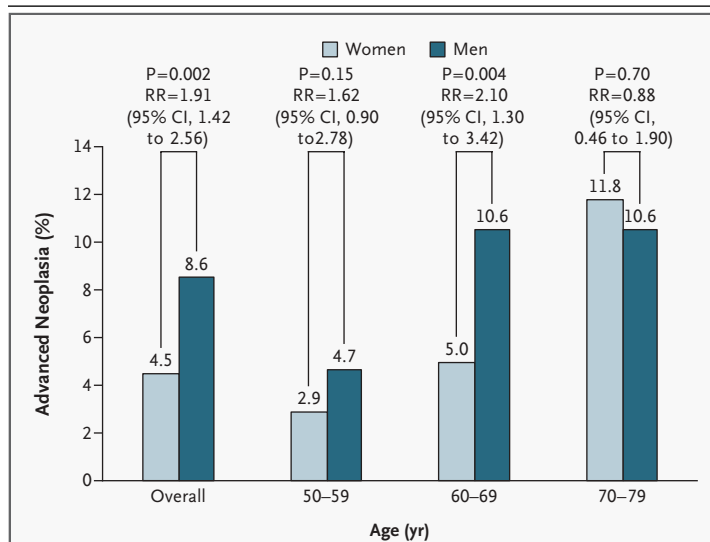


Figure 1. Prevalence of Advanced Neoplasia among Men and Women with a Negative Fecal Occult-Blood Test and No Family History of Colon Cancer, According to Age.

The women were from the current study, and the men were from VA Cooperative Study 380. The relative risk (RR) is for men as compared with women. CI denotes confidence interval.

DISCUSSION

We evaluated the diagnostic yield of screening colonoscopy in asymptomatic women who were referred for colorectal-cancer screening. After matching the women in the current study with men from VA Cooperative Study 380 for a normal fecal occult-blood test and the absence of a family history of colon cancer, we found that almost twice as many cases of advanced colorectal neoplasia were detected in the men, and the prevalence of advanced neoplasia among women who were 50 to 59 years old was less than 3 percent (Fig. 1). Given these findings, it might be argued that screening flexible sigmoidoscopy is more appropriate than colonoscopy for women who are 50 to 59 years old. However, our data also indicate that the diagnostic yield of flexible sigmoidoscopy for advanced neoplasia is much lower among women than among men (35.2 percent vs. 66.3 percent, $P<0.001$). Thus, advanced neoplasia would have been missed in 65 percent of women with advanced neoplasia if they had undergone flexible sigmoidoscopy alone. Also, women

without distal-colon neoplasia and women with distal-colon neoplasia had similar prevalences of advanced neoplasia in the proximal colon (3.4 percent and 3.2 percent, respectively; $P=1.00$). On the basis of these data, we believe that colonoscopy is the preferred method of screening for colorectal cancer in women and that flexible sigmoidoscopy is an inadequate method of predicting advanced neoplasia in the proximal colon in women.

A comparison of the findings in this study and those in VA Cooperative Study 380 provides data on the variation in the prevalence and phenotypic expression of advanced neoplasia according to age and sex. The prevalence of advanced neoplasia was greater among men than among women in the age group of 60 to 69 years ($P=0.004$), and there was a trend toward a higher prevalence among men in the group of men and women who were 50 to 59 years old ($P=0.15$) but not in the group of men and women who were at least 70 years old ($P=0.70$). This finding suggests that biologic or behavioral factors inherent in women delay the formation of advanced neoplasia. The lower diagnostic yield of flexible sigmoidoscopy among women suggests that there is a right-sided shift for advanced neoplasia in women as compared with men.

Our data indicate that the diagnostic yield of flexible sigmoidoscopy is significantly lower among women 50 to 59 years old than among men in this age group (Fig. 2) and that 70 percent of cases of advanced colorectal neoplasia among women in this age group would be missed if they were to undergo flexible sigmoidoscopy alone. Although advanced colonic neoplasia is less common in average-risk women than in average-risk men who are 50 to 59 years of age (2.9 percent vs. 4.7 percent), more cases would be missed in such women than in their male counterparts (2.0 percent vs. 1.3 percent), if flexible sigmoidoscopy alone were performed. Therefore, flexible sigmoidoscopy appears to be a much more effective screening tool in men than in women. Since previous cost-effectiveness analyses²²⁻²⁴ have been hampered by the lack of precise data on the prevalence of adenomas and advanced neoplasia in men and women, our data may be used to define the cost-effectiveness of screening colonoscopy among women and men.

Our study has methodologic limitations. We used colonoscopic findings in the distal colon as a surrogate for the findings with flexible sigmoidoscopy. Therefore, our data on flexible sigmoidoscopic findings are estimates. Since patients were

sedated before undergoing vigorous colonic lavage and then colonoscopy, which was performed by expert endoscopists, our estimated yield of flexible sigmoidoscopy for distal-colon neoplasia might be higher than that associated with flexible sigmoidoscopy performed in the absence of sedation and by less experienced endoscopists after less vigorous colonic lavage.

In conclusion, we acknowledge that the implementation of national and international colonoscopic-screening programs may be constrained by limitations in the availability of endoscopic resources and in insurance coverage.^{8,9} Although the use of colonoscopic screening is becoming widespread in the United States, it is not widely used in any other country. In other countries, the use of one-time flexible sigmoidoscopy is being pursued as a means to reduce the risk of colorectal cancer.²⁵ Given the lack of consensus about the preferred tool for colorectal-cancer screening, we should use the best available information to guide our patients' choices. Our study indicates that the majority of cases of advanced neoplasia in women would be missed if they underwent flexible sigmoidoscopy alone. In our opinion, colonoscopy is the preferred method of colorectal-cancer screening in average-risk, asymptomatic women.

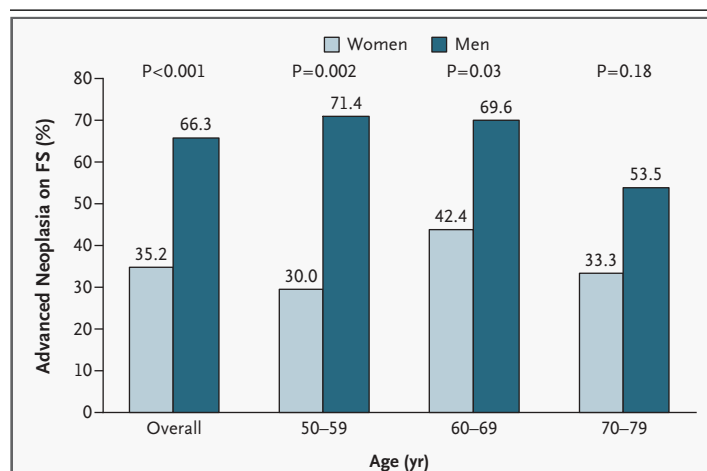


Figure 2. Yield of Flexible Sigmoidoscopy (FS) for Advanced Colorectal Neoplasia Anywhere in the Colon in Men and Women, According to Age.

The yield of FS was defined as the proportion of patients with advanced colorectal neoplasia who were found to have advanced lesions in the distal colon or advanced lesions in the proximal colon along with small adenomas in the distal colon, which would have triggered the performance of colonoscopy. The women were from the current study, and the men were from VA Cooperative Study 380.

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APPENDIX

In addition to the authors, the following investigators participated in the CONCeRN Study: J. Butler, P. Perdue, and P.J. Chandler, Be-

thesda, Md.; C. Furlong, Portsmouth, Va.; and J. Shad and R. Schindler, San Diego, Calif.

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